REMARKS

Claims 1-5 are pending.

Inventorship

The Examiner asserts that the request for deletion of an inventor previously submitted in the present application was deficient because it was not accompanied by the statement required under 37 C.F.R. §1.48(b)(2) that the deletion is required because claims have been amended or canceled such that he or she is no longer an inventor of any remaining claim in the nonprovisional application. Applicants note that page 5 of the Amendment and Response to Office Action mailed September 14, 2004 stated that the deleted inventors' inventions are no longer being claimed in the present application as a result of prosecution. Applicants maintain that this statement satisfies the requirements of 37 C.F.R. §1.48(b)(2). Accordingly, Applicants respectfully request that the inventorship be amended as requested in the previous Amendment and Response to Office Action.

Priority

The Examiner asserts that the present application is entitled to a priority date of May 2, 2002. Applicants reiterate that the instant application is a continuation of, and claims priority under 35 U.S.C. § 120 to, US Application 10/006867 filed 12/6/2001, which is a continuation of, and claims priority under 35 U.S.C. § 120 to, PCT Application PCT/US00/23328 filed 8/24/2000, which is a continuation-in-part of, and claims priority under 35 U.S.C. § 120 to, US Application 09/380137 filed 8/25/1999, which is the National Stage filed under 35 U.S.C. § 371 of PCT Application PCT/US99/12252 filed 6/2/1999, which claims priority under 35 U.S.C. § 119 to US Provisional Application 60/090862 filed 6/26/1998. As discussed below, Applicants maintain that the claimed invention does possess utility and that the present application is entitled to a priority date as of June 26, 1998.

Rejections Under 35 U.S.C. §101 and 35 U.S.C. §112

Claims 1-5 were rejected under 35 U.S.C. §101 as lacking utility for the reasons set forth in the previous Office Action. Claims 1-5 were also rejected as not being enabled by the specification because the claimed invention lacks utility.

The Examiner asserts that while the polynucleotide encoding PRO1115 is more highly expressed in normal stomach tissue or normal lung tissue compared to stomach tumor or lung

tumor respectively, Applicants have not provided evidence showing that this polypeptide is more highly expressed in normal tissue. The Examiner cites Pennica et al. as supporting a lack of correlation between DNA amplification and increased gene expression. In addition, the Examiner again notes that cancerous tissue can be aneuploid and asserts that the data in the specification has not been corrected for aneuploidy.

The Examiner cites Haynes et al. for the proposition that polypeptide levels cannot accurately be predicted from mRNA levels. Hu et al. is also cited to show that for genes displaying a 5-fold change or less in tumors compared to normal tissue there was no evidence of correlation between altered gene expression and a known role in the disease.

The Examiner asserts that given the increase in amplified DNA (copy number) for PRO1115 in normal stomach tissue or normal lung tissue compared to stomach tumor or lung tumor respectively and the evidence provided in the current literature, one skilled in the art would not assume that a higher expression would correlate with increased mRNA or polypeptide levels.

The Examiner further asserts that the statements in the Declaration signed by Mr. Grimaldi are the declarant's opinion and are not supported by fact or evidence. According to the Examiner, there has been no distinction between total nucleic acid, which includes chromosomal DNA, and mRNA. The Examiner maintains that there is no description in the specification that would indicate a correlation with higher expression level of the message to PRO1115. The Examiner asserts that there is no information on the record as to whether the encoded protein is expressed at all in stomach tissue and lung tissue, cancerous or otherwise. The Examiner cites Pennica for the proposition that there is no predictable correlation between copy number and polypeptide levels.

The Examiner maintains that the statements in Dr. Polakis' Declaration are unsupported by evidence. In addition, the Examiner asserts that the Orntoft reference submitted in the response to the previous Office Action did not look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. The Examiner maintains that it is not clear whether or not PRO1115 is in a gene cluster in a region of a chromosome that is highly amplified. The Examiner asserts that the Hyman reference submitted with the response to the previous Office Action indicates that less than half of highly amplified genes showed

overexpression. The Examiner maintains that the Pollack reference submitted with the response to the previous Office Action concentrates on large chromosomal regions showing high amplification and that Pollack did not show a relationship between amplification and polypeptide expression. The Examiner concludes that the submitted references do not teach that there is a direct correlation between increased mRNA levels and increased levels of encoded protein. In addition, the Examiner asserts that the Hanna reference submitted with the response to the previous Office Action supports the Examiner's position that gene amplification does not reliably correlate with polypeptide overexpression.

The Examiner asserts that the statements in Mr. Grimaldi's Declaration are the declarant's own opinion and that one cannot determine whether the observed "amplification" of nucleic acids is due to an increase in copy number or in transcription rates. The Examiner maintains that the specification provides no information regarding increased mRNA levels of PRO1115 in normal stomach tissue and normal lung tissue samples compared to stomach tumor or lung tumor respectively.

The Examiner asserts that the submitted Declaration does not provide data such that the Examiner can independently draw conclusions. The Examiner maintains that there is no evidentiary art that corroborates that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. The Examiner also maintains that the literature cautions against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. The Examiner asserts that it is not known whether PRO1115 is expressed in normal stomach and normal lung tissue and what the relative levels of expression are.

The Examiner states that although the Declaration of Dr. Polakis states that it is a central dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide, the specification provides no information regarding differential mRNA levels of PRO1115 in tumor samples as contrasted to normal tissue samples or the corresponding protein levels. The Examiner asserts that the Declarations do not provide data such that the Examiner can independently draw conclusions. The Examiner notes that the Hu reference cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue.

The Examiner asserts that the statements in the Ashkenazi Declaration did not demonstrate utility because there is no evidence whether the polypeptide is overexpressed. The Examiner further asserts that the differential expression data may be an indication that the cancer tissue is aneuploid.

The Examiner asserts that the Haynes and Hu references contradict Applicants assertion that there is a direct correlation between mRNA levels and the expression of the encoded protein. The Examiner further maintains that Pennica supports the PTO's position that there is no correlation between DNA amplification and gene expression.

Applicants respectfully traverse.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added).

The mere consideration that further experimentation might be performed to more fully develop the claimed subject matter does not support a finding of lack of utility. M.P.E.P. § 2107.01 III cites *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) in stating

that "Usefulness in patent law ... necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." Further, "[T]o violate § 101 the claimed device must be totally incapable of achieving a useful result" *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999), *citing Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed.Cir.1992).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, in assessing the credibility of the asserted utility, the M.P.E.P. states that "to overcome the presumption of truth that an assertion of utility by the applicant enjoys" the PTO must establish that it is "more likely than not that one of ordinary skill in the art would doubt (i.e., "question") the truth of the statement of utility." M.P.E.P. § 2107.02 III A. The M.P.E.P. cautions that:

> Rejections under 35 U.S.C. 101 have been **rarely sustained** by federal courts. Generally speaking, **in these rare cases**, the 35 U.S.C. 101 rejection was sustained either because the **applicant ... asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art**. M.P.E.P. § 2107.02 III B. (underline emphasis in original, bold emphasis added); citing *In re Gazave*, 379 F.2d 973, 978, 154 USPQ 92, 96 (CCPA 1967).

Utility need NOT be Proved to a Statistical Certainty – a Reasonable Correlation between the Evidence and the Asserted Utility is Sufficient

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a

question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

> [T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

While the *Fujikawa* case was in the context of utility for pharmaceutical compounds, the principals stated by the Court are applicable in the instant case where the asserted utility is for a diagnostic use – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art "to a reasonable probability." In addition, the

evidence need not be direct, so long as there is a "sufficient correlation" between the tests performed and the asserted utility.

The Court in *Fujikawa* relied in part on its decision in *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985). In *Cross*, the Appellant argued that basic *in vitro* tests conducted in cellular fractions did not establish a practical utility for the claimed compounds. Appellant argued that more sophisticated *in vitro* tests using intact cells, or *in vivo* tests, were necessary to establish a practical utility. The Court in *Cross* rejected this argument, instead favoring the argument of the Appellee:

> [*I*]*n vitro* results...are generally predictive of *in vivo* test results, i.e., there is a **reasonable correlation** therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. [Appellee] has not urged, and rightly so, that there is an invariable exact correlation between *in vitro* test results and *in vivo* test results. Rather, [Appellee's] position is that successful *in vitro* testing for a particular pharmacological activity establishes a **significant probability** that *in vivo* testing for this particular pharmacological activity will be successful. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (emphasis added).

The *Cross* case is very similar to the present case. Like *in vitro* testing in the pharmaceutical industry, those of skill in the field of biotechnology rely on the reasonable correlation that exists between gene expression and protein expression (see below). Were there no reasonable correlation between the two, the techniques that measure gene levels such as microarray analysis, differential display, and quantitative PCR would not be so widely used by those in the art. As in *Cross*, Applicants here do not argue that there is "an invariable exact correlation" between gene expression and protein expression. Instead, Applicants' position detailed below is that a measured change in gene expression in cancer cells establishes a "significant probability" that the expression of the encoded polypeptide in cancer will also be changed based on "a reasonable correlation therebetween."

Taken together, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true**. The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not those skilled in the art, to a reasonable probability, would believe that the claimed invention is useful as a diagnostic tool or therapeutic tool for cancer.

Substantial Utility

Summary of Applicants' Arguments and the PTO's Response

In an attempt to clarify Applicants' argument, Applicants offer a summary of their argument and the disputed issues involved. Applicants assert that the claimed antibodies have utility as diagnostic tools for cancer, particularly stomach tumor and lung tumor. Applicants are not asserting that the claimed antibodies necessarily provide a definitive diagnosis of stomach cancer and lung cancer, but rather that they are useful, alone or in combination with other diagnostic tools to assist in the diagnosis of stomach cancer and lung cancer. Applicants' asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO1115 polypeptide is more highly expressed in normal stomach tissue or normal lung tissue compared to stomach tumor or lung tumor respectively;

2. Applicants assert that it is well-established in the art that a change in the level of mRNA for a particular protein, e.g. a decrease, generally leads to a corresponding change in the level of the encoded protein, e.g. a decrease;

3. Given Applicants' evidence that the level of mRNA for the PRO1115 polypeptide is decreased in stomach tumor or lung tumor compared to normal stomach tissue or normal lung tissue respectively, it is likely that the PRO1115 polypeptide is differentially expressed in stomach tumors and lung tumors. Therefore the PRO1115 polypeptide can be used to generate antibodies which are useful as diagnostic tools to distinguish tumor from normal tissue.

Applicants understand the PTO to be making several arguments in response to Applicants' asserted utility:

1. The PTO asserts that given the increase in amplified DNA (copy number) for PRO1115 in normal stomach tissue or normal lung tissue compared to stomach tumor or lung

tumor respectively, one skilled in the art would not assume that a higher expression would correlate with increased mRNA or polypeptide levels; and

2. The PTO asserts that mRNA over-expression does not correlate with protein over-expression.

As detailed below, Applicants submit that the PTO has failed to meet its initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). First, Applicants submit that Example 18 establishes that the mRNA encoding the PRO1115 polypeptide is more highly expressed in normal stomach tissue or normal lung tissue compared to stomach tumor or lung tumor respectively. Second, Applicants maintain that given the well-established correlation between a change in the level of mRNA with a corresponding change in the levels of the encoded protein, the PRO1115 protein is likely to be differentially expressed in stomach tumors or lung tumors. Thus the claimed antibodies are useful as cancer diagnostic tools. Finally, even if the PTO has met its initial burden, Applicants have submitted enough rebuttal evidence to establish that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true. As stated above, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not statistical or absolute certainty.**

Applicants have established that the Gene Encoding the PRO1115 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue

Applicants first reiterate that the mRNA encoding the PRO1115 polypeptide is more highly expressed in normal stomach tissue or normal lung tissue compared to stomach tumor or lung tumor respectively.

The gene expression data in the specification, Example 18, shows that the mRNA associated with protein PRO1115 was more highly expressed in normal stomach tissue or normal lung tissue compared to stomach tumor or lung tumor respectively. Gene expression was analyzed using standard semi-quantitative PCR amplification reactions of cDNA libraries isolated from different human tumor and normal human tissue samples. Because cDNA libraries are prepared by isolating mRNA from a particular tissue and converting it to the corresponding cDNA, the expression data in Example 18 reflect levels of mRNA in the tested tissue types

rather than chromosomal gene copy number. Identification of the differential expression of the PRO1115 polypeptide-encoding gene in tumor tissue compared to the corresponding normal tissue renders antibodies which bind the PRO1115 polypeptide useful as a diagnostic tool for the determination of the presence or absence of tumor. In support, Applicants previously submitted as Exhibit 1 a first Declaration of J. Christopher Grimaldi, an expert in the field of cancer biology. This declaration explains the importance of the data in Example 18, and how differential gene and protein expression studies are used to differentiate between normal and tumor tissue (see Declaration, paragraph 7).

In paragraph 5 of his declaration, Mr. Grimaldi states that the gene expression studies reported in Example 18 of the instant application were made from pooled samples of normal and of tumor tissues. Mr. Grimaldi explains that:

> The DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. *Data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual.* That is, the detection of variations in gene expression is likely to represent a more generally relevant condition when pooled samples from normal tissues are compared with pooled samples from tumors in the same tissue type. (Paragraph 5) (emphasis added).

In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or under-expressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. Thus, the results of Example 18 reflect at least a two-fold difference between normal and tumor samples. He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal," thus establishing their reliability. He explains that, contrary to the PTO's assertions, "The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (Paragraph 7). Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. As Mr. Grimaldi states, "If a difference is detected, this indicates

that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor."

Applicants submit that Mr. Grimaldi is an expert in the field and conducted or supervised the experiments at issue. Applicants remind the PTO that "[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned." PTO Utility Examination Guidelines (2001) (emphasis added). In addition, declarations relating to issues of fact should not be summarily dismissed as "opinions" without an adequate explanation of how the declaration fails to rebut the Examiner's position. *In re Alton* 76 F.3d 1168 (Fed. Cir. 1996).

In conclusion, Applicants submit that the evidence reported in Example 18, combined with the first Grimaldi Declaration, establish that there is at least a two-fold difference in PRO1115 cDNA between stomach tumor or lung tumor and normal stomach tissue or normal lung tissue respectively. The PTO has not offered any significant arguments or evidence to the contrary. As Applicants explain below, it is more likely than not that the PRO1115 polypeptide is also differentially expressed in stomach tumor or lung tumor, and can therefore be used to distinguish stomach tumor or lung tumor from normal stomach tissue or normal lung tissue respectively. This provides utility for the claimed antibodies.

Applicants have established that the Accepted Understanding in the Art is that there is a Direct Correlation between mRNA Levels and the Level of Expression of the Encoded Protein

Applicants next turn to the second portion of their argument in support of their asserted utility – that it is well-established in the art that a change in the level of mRNA for a particular protein, generally leads to a corresponding change in the level of the encoded protein; given Applicants' evidence of differential expression of the mRNA for the PRO1115 polypeptide in stomach tumor or lung tumor, it is more likely than not that the PRO1115 polypeptide is differentially expressed; and antibodies which bind to polypeptides which are differentially expressed in stomach tumors have utility as diagnostic tools.

In support of the assertion that changes in mRNA are positively correlated to changes in protein levels, Applicants previously submitted a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology (previously attached as Exhibit 2). As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast

majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants also previously submitted a copy of the declaration of Paul Polakis, Ph.D. (previously attached as Exhibit 3), an expert in the field of cancer biology. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion, based on over 20 years of scientific research, that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

Applicants submit that Mr. Grimaldi and Dr. Polakis are experts in the field and conducted or supervised the experiments at issue. Applicants remind the PTO that "[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned." PTO Utility Examination Guidelines (2001) (emphasis added). In addition, declarations relating to issues of fact should not be summarily dismissed as "opinions" without an adequate explanation of how the declaration fails to rebut the Examiner's position. *In re Alton* 76 F.3d 1168 (Fed. Cir. 1996).

The statements of Grimaldi and Polakis are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) (submitted herewith as Exhibit 1) and (4th ed. 2002) (submitted herewith as Exhibit 2)). Figure 9-2 of Exhibit 1 shows the steps at which eukaryotic gene expression can be controlled. The first step depicted is transcriptional control. Exhibit 1 provides that "[f]or most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized." Exhibit 1 at 403 (emphasis added). In addition, the text states that "Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made." Exhibit 1 at 453 (emphasis added). Thus, as established in Exhibit 1, the predominant mechanism for regulating the amount of protein produced is by regulating transcription initiation.

In Exhibit 2, Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." Exhibit 2 at 302 (emphasis added). Similarly, Figure 6-90 on page 364 of Exhibit 2 illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Exhibit 2 at 364 (emphasis added). This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Exhibit 2 at 379 (emphasis added).

Further support for Applicants' position can be found in the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)) (submitted herewith as Exhibit 3) which states "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (emphasis added).

Additional support is also found in Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004, submitted herewith as Exhibit 4. Zhigang studied the expression of prostate stem cell antigen (PSCA) protein and mRNA to validate it as a potential molecular target for diagnosis and treatment of human prostate cancer. The data showed "a high degree of correlation between PSCA protein and mRNA expression" Exhibit 4 at 4. Of the samples tested, 81 out of 87 showed a high degree of correlation between mRNA expression and protein expression. The authors conclude that "it is demonstrated that PSCA protein and mRNA overexpressed in human prostate cancer, and that the increased protein level of PSCA was resulted from the upregulated transcription of its mRNA." Exhibit 4 at 6. Even though the correlation between mRNA expression and protein expression occurred in 93% of the samples tested, not 100%, the authors state that "PSCA may be a promising molecular marker for the clinical prognosis of human Pca and a valuable target for diagnosis and therapy of this tumor." Exhibit 4 at 7.

Further, Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002), submitted herewith as Exhibit 5, states the following:

> The **fundamental principle** of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells...[M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Meric *et al.* at 971 (emphasis added).

Those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression.

Together, the declarations of Grimaldi and Polakis, the accompanying references, and the excerpts and references provided above all establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein.

The Examiner cites Pennica et al. as supporting a lack of correlation between DNA amplification and increased gene expression. In addition, the Examiner notes that Sen teaches that cancerous tissue can be aneuploid and asserts that the data in the specification has not been corrected for aneuploidy.

Applicants note that although it is true that cancerous tissue is sometimes aneuploid, Pennica relates to gene amplification (i.e. increased copy number). In contrast, the data in Example 18 was obtained by performing quantitative PCR on cDNA libraries. Thus, as discussed above, the data in Example 18 reflects mRNA levels rather than copy number. Furthermore, as noted in the previous Amendment and Response to Office Action, Pennica does not look at protein levels and does not address the relationship between mRNA levels and polypeptide levels.

Applicants reiterate that whether or not the cells are aneuploid is irrelevant to the utility of the claimed invention because regardless of whether the differential mRNA levels demonstrated in Example 18 are a result of increased copy number or increased rates of transcription, the fact remains that the polypeptides recognized by the claimed antibodies are differentially expressed. Applicants maintain that antibodies to differentially expressed polypeptides are useful as diagnostic markers for cancer.

The Examiner asserts that Haynes et al. (1998, *Electrophoresis*, 19:1862-1871) found that polypeptide levels cannot be accurately predicted from mRNA levels when studying protein expression in *Saccharomyces cerevisiae*. In particular, the Examiner points to the finding that, for some genes, equivalent mRNA levels translated into protein abundances which varied by more than 50-fold.

Applicants submit that Haynes does not contradict the utility or enablement of the instant claims. Haynes is a review article dealing with the art of proteome analysis. The assertions in Haynes cited by the Examiner were made in an effort to identify shortcomings in the art of mRNA quantification to argue for "proteome analysis to become an essential component in the comprehensive analysis of biological systems." Haynes, p. 1863. Haynes studied 80 selected samples from *Saccharomyces cerevisiae*, and reported "a general trend but no strong correlation between protein and transcript levels (Fig. 1)." Id. However, a cursory inspection of Fig. 1 shows a clear correlation between the mRNA levels and protein levels measured. This correlation is confirmed by an inspection of the full-length research paper from which the data in Fig. 1 were derived, presented herein as Exhibit 6 (Gygi et al., Molecular and Cellular Biology, Mar. 1999, 1720-1730). Gygi states that "there was a general trend of increased protein levels resulting from increased mRNA levels," with a correlation coefficient of 0.935, indicating a

strong correlation. Gygi, p. 1726. Moreover, Gygi also states that the correlation is especially strong for highly expressed mRNAs. Id. Considering that Example 18 of the specification shows higher expression of PRO1115 mRNA in normal stomach or normal lung as compared to stomach tumor or lung tumor respectively, Haynes and Gygi actually provide strong evidence in support of a general correlation between mRNA and protein levels, and thus the utility of the claimed antibodies to PRO1115 polypeptides.

The 50-fold variation referred to by the Haynes reference and cited by the Examiner, does not in any way show the absence of a correlation between mRNA and protein levels, but rather identifies the outer limits of variability in the authors' experiments. This variability may support the authors' assertion that the amount of a particular protein cannot accurately predict the particular level of the corresponding mRNA transcript, but it does not suggest an absence of a general correlation between mRNA and protein levels. Again, Applicants' utility is based on the differential expression of mRNA in normal stomach or normal lung versus stomach tumor or lung tumor respectively. Exact levels of expression are irrelevant. Moreover, Gygi states that the high degree of variability seen at low levels of mRNA (shown in inset of Fig. 1, Haynes p. 1863) is due to the fact that "the magnitude of the error in the measurement of mRNA levels is inversely proportional to the mRNA levels." Gygi, p. 1727. Considering that PRO1115 mRNA has been shown in Example 18 of the specification to be more highly expressed in normal stomach tissue or normal lung tissue than stomach tumor or lung tumor respectively, the variability identified by Haynes is even less applicable to establishing the absence of a correlation between mRNA and protein levels in the instant case.

As stated above, the standard for utility is not absolute certainty, but rather whether one of skill in the art would be more likely than not to believe the asserted utility. Here, the utility of antibodies which bind to PRO1115 polypeptides as diagnostic tools does not require Applicants to show that mRNA levels correlate to protein levels in every case, but rather only that the correlation exists more often than not. The data presented in Haynes is not inconsistent with or contradictory to the utility or enablement of the instant claims. To the contrary, the data clearly show a general correlation between protein levels and mRNA levels, and thus support Applicants' assertion that such a general correlation exists.

Even if Haynes supported the Examiner's argument, which it does not, one contrary example does not establish that one of skill in the art would find it is more likely than not there is no general correlation between mRNA level and protein levels. In fact, the working hypothesis among those skilled in the art, as illustrated by the evidence presented above by Applicants, is that there is a direct correlation between mRNA levels and protein levels. This is further supported by the statement in Haynes that "interpretations of quantitative mRNA expression profiles frequently implicitly or explicitly assume that for specific genes the transcript levels are indicative of the levels of protein expression." See, Haynes, p. 1863, first full paragraph. Haynes does not suggest there is no correlation between mRNA and protein levels, but rather points to what the authors believe are shortcomings of using mRNA quantification to predict protein levels; specifically, that mRNA levels may not accurately predict protein levels *in each particular instance*. Considering the more likely than not standard for utility, Haynes' identification of reasons why proteomic analysis may be preferable in some cases does not contradict Applicants' evidence that there is a general correlation between mRNA and protein levels.

In Hu, the researchers used an automated literature-mining tool to summarize and estimate the relative strengths of all human gene-disease relationships published on Medline. They then generated a microarray expression dataset comparing breast cancer and normal breast tissue. Using their data-mining tool, they looked for a correlation between the strength of the literature association between the gene and breast cancer, and the magnitude of the difference in expression level. They report that for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a *known* role in the disease. *See* Hu at 411. However, among genes with a 10-fold or more change in expression level, there was a strong correlation between expression level and a *published* role in the disease. *Id.* at 412. Importantly, Hu reports that the observed correlation was only found among estrogen receptor-positive tumors, not ER-negative tumors. *Id.*

The general findings of Hu are not surprising – one would expect that genes with the greatest change in expression in a disease would be the first targets of research, and therefore have the strongest known relationship to the disease as measured by the number of publications reporting a connection with the disease. The correlation reported in Hu only indicates that the

greater the change in expression level, the more likely it is that there is a *published* or *known* role for the gene in the disease, as found by their automated literature-mining software. Thus, Hu's results merely reflect a bias in the literature toward studying the most prominent targets, and reflect nothing regarding the ability of a gene that is 2-fold or more differentially expressed in tumors to serve as a disease marker. Hu acknowledges the shortcomings of this method in explaining the disparity in Hu's findings for ER-negative versus ER-positive tumors: Hu attributes the "bias in the literature" toward the more prevalent ER-positive tumors as the explanation for the lack of any correlation between number of publications and gene expression levels in less-prevalent (and, therefore, less studied) ER-negative tumors. *Id.* Because of this intrinsic bias, Hu's methodology is unlikely to ever note a correlation of a disease with less differentially-expressed genes and their corresponding proteins, regardless of whether or not an actual relationship between the disease and less differentially-expressed genes exists. Accordingly, Hu's methodology yields results that provide little or no information regarding biological significance of genes with less than 5-fold expression change in disease. As discussed above, Applicants maintain that the data in Example 18 is significant.

The Examiner asserts that given the increase in amplified DNA (copy number) for PRO1115 in the normal stomach tissue or normal lung tissue compared to stomach tumor or lung tumor and the evidence provided in the current literature, one skilled in the art would not assume that a higher expression would correlate with increased mRNA or polypeptide levels.

As discussed above, Applicants note that the data in Example 18 does not reflect an increase in copy number but instead relates to mRNA levels. In addition, as discussed above, Applicants maintain that those skilled in the art would believe that it is more likely than not that because the mRNA encoding the polypeptides recognized by the claimed antibodies is differentially expressed, the encoded polypeptides are also differentially expressed.

The Examiner asserts that the statements in the Declaration signed by Mr. Grimaldi are the declarant's opinion and are not supported by fact or evidence. The Examiner also asserts that there has been no distinction between total nucleic acid, which includes chromosomal DNA and mRNA. The Examiner maintains that there is no description in the specification that would indicate a correlation with higher expression level of the message to PRO1115. The Examiner asserts that there is no information on the record as to whether the PRO1115 protein is expressed

at all in stomach tissue or lung tissue. The Examiner cites Pennica for the proposition that there is no predictable correlation between copy number and polypeptide levels.

As discussed above, Applicants note that the statements in the Declaration signed by Mr. Grimaldi are not simply his personal opinion but are based on a large body of scientific data. In particular, as noted in the Grimaldi Declaration, a variety of techniques founded on the principle that polypeptide expression levels correlate with mRNA levels have become widely used. These include Northern Blotting, Differential Display, *in situ* hybridization, quantitative PCR, Taqman and microarray technology. As pointed out in the Grimaldi Declaration, such methodology would have little value if protein expression levels did not correlate with mRNA levels. In addition, the Grimaldi Declaration states that such techniques have identified a large number of genes in which differential levels of mRNA expression correspond to differential levels of protein expression. Thus, the Grimaldi Declaration does not represent Mr. Grimaldi's personal opinion but instead is his conclusion based on a large body of scientific data.

In addition, as discussed above, Applicants note that whether or not increased mRNA levels correlate with increased polypeptide levels is an issue of fact. Declarations relating to issues of fact should not be summarily dismissed as "opinions" without an adequate explanation of how the Declaration fails to rebut the Examiner's position. *In re Alton* 76 F.3d 1168 (Fed. Cir. 1996). Applicants submit that Mr. Grimaldi is an expert in the field and conducted or supervised the experiments at issue. Applicants remind the PTO that "[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned." PTO Utility Examination Guidelines (2001) (emphasis added). The PTO has not supplied any reasons or evidence to question the accuracy of the facts upon which Mr. Grimaldi based his opinion. Mr. Grimaldi has personal knowledge of the relevant facts, has based his opinion on those facts, and the PTO has offered no reason or evidence to reject either the underlying facts or his opinion. Therefore, the PTO should accept Mr. Grimaldi's opinion that increased mRNA levels correlate with increased polypeptide levels. Furthermore, Applicants note that the position of Mr. Grimaldi is supported by the Alberts textbook, the Zhigang reference, the Meric textbook, and the Lewin textbook discussed above.

With respect to the Examiner's citation of Pennica, as discussed above Applicants note that the data in the specification reflect mRNA levels, not gene copy number. Furthermore, as

discussed above, Pennica does not look at protein levels and does not address the relationship between mRNA levels and polypeptide levels.

The Examiner asserts that the Orntoft reference submitted in the response to the previous Office Action did not look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. The Examiner also asserts that it is not clear whether or not PRO1115 is in a gene cluster in a region of a chromosome that is highly amplified. The Examiner asserts that the Hyman reference submitted with the response to the previous Office Action indicates that less than half of highly amplified genes showed overexpression. The Examiner maintains that the Pollack reference submitted with the response to the previous Office Action concentrates on large chromosomal regions showing high amplification and that Pollack did not show a relationship between amplification and polypeptide expression. The Examiner concludes that the submitted references do not teach that there is a direct correlation between increased mRNA levels and increased levels of encoded protein. In addition, the Examiner asserts that the Hanna reference submitted with the response to the previous Office Action supports the Examiner's position that gene amplification does not reliably correlate with polypeptide overexpression.

Applicants note that, as discussed above, the data in Example 18 reflect mRNA levels, not gene copy number and, as discussed above, the claimed antibodies are useful as diagnostics or therapeutics regardless of whether or not gene amplification plays any role in the overexpression of the polypeptide. In addition, Applicants note that Orntoft did look at mRNA and protein levels for individual genes located within amplified or deleted chromosomal regions and found that of the 40 proteins analyzed only one showed disagreement between transcript alteration and protein alteration (Orntoft, page 42). Hyman looked at the correlation between gene copy number and mRNA levels and did not look at polypeptide levels. However, Hyman observed that "the results illustrate a considerable influence of copy number on gene expression patterns." The Pollack reference also examined the mRNA levels of individual genes within amplified regions, although polypeptide levels were not examined. Pollack concluded "that on average a 2-fold change in copy number is associated with a corresponding 1.5-fold change in mRNA levels." (Pollack, abstract) Applicants further note that the Hanna reference states that "In general FISH and IHC results correlate well," indicating that while it may be beneficial to look at both gene amplification and protein levels, in general the two are correlated.

The Examiner asserts that the statements in Mr. Grimaldi's Declaration are the declarant's own opinion and that one cannot determine whether the observed "amplification" of nucleic acids is due to an increase in copy number or in transcription rates. The Examiner also asserts that the specification provides no information regarding increased mRNA levels of PRO1115 in normal stomach or lung tissue samples compared to stomach or lung tumor.

As discussed above, Applicants note that Mr. Grimaldi is an expert in the field. In addition, whether or not increased mRNA levels correlate with increased polypeptide levels is an issue of fact. As discussed above, Declarations relating to issues of fact should not be summarily dismissed as "opinions" without an adequate explanation of how the Declaration fails to rebut the Examiner's position. *In re Alton* 76 F.3d 1168 (Fed. Cir. 1996). Furthermore, as discussed above, Applicants remind the PTO that "[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned." PTO Utility Examination Guidelines (2001) (emphasis added).

In addition, the data in Example 18 reflect mRNA levels not gene copy number, and that, as discussed above, the claimed antibodies which bind to differentially expressed polypeptides have utility regardless of whether the polypeptides are differentially expressed as a result of gene amplification or as a result of differential transcription. Applicants maintain that, as discussed above, one skilled in the art would believe that it is more likely than not that the observed increase in mRNA levels would result in an increase in polypeptide levels.

The Examiner asserts that the submitted Declaration does not provide data such that the Examiner can independently draw conclusions. The Examiner also asserts that there is no evidentiary art that corroborates that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. The Examiner maintains that the literature (Haynes et al. and Hu et al.) cautions against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. The Examiner asserts that it is not known whether PRO1115 is expressed in normal stomach or normal lung and what the relative levels of expression are.

Applicants note that the statement that any visually detectable difference between two samples is indicative of at least a two-fold difference in cDNA is a statement of scientific fact.

As discussed above, a declaration that is filed to address a question of fact must be considered by the Examiner and if the Examiner maintains his rejection, he must be able to explain why the declaration fails. *In re Alton* 76 F.3d 1168 (Fed. Cir. 1996). Applicants also remind the PTO that "[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned." PTO Utility Examination Guidelines (2001) (emphasis added). Applicants submit that the Examiner has not offered any reason to dispute the statements in the Declaration. Furthermore, Applicants provide herewith as Exhibit 7 a copy of page 122 of the 2002-2003 New England Biolabs catalog. Exhibit 7 shows DNA size markers of differing lengths run on an agarose gel. The column on the left provides the mass of each marker in nanograms and the column on the right provides the length of the marker. It is apparent that the band intensity of markers having mass differences of two fold are readily distinguishable by eye (See for example, the difference in band intensities of the 0.1kb fragment present at 61ng and the 0.5kb marker present at 124ng). Accordingly, Applicants maintain that the procedures used to detect differences in expression levels were sufficiently sensitive to detect two-fold differences.

With respect to the Haynes et al. and Hu et al. references, as discussed above, Applicants maintain that these references do not refute Applicants' position that it is more likely than not that a polypeptide encoded be a differentially expressed mRNA will be differentially expressed.

The Examiner states that although the Declaration of Dr. Polakis states that it is a central dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide, the specification provides no information regarding increased mRNA levels of PRO1115 in tumor samples as contrasted to normal tissue samples or the corresponding protein levels. The Examiner asserts that the Declarations do not provide data such that the Examiner can independently draw conclusions. The Examiner notes that the Hu reference cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue.

Applicants note that the data in Example 18 demonstrate that the polypeptides recognized by the claimed antibodies are encoded by mRNAs which are expressed at a higher level in normal stomach and lung than in stomach and lung tumor. Furthermore, Applicants note that the Declaration of Dr. Polakis indicates that experiments in which the levels of proteins encoded by

mRNAs that are overexpressed were analyzed demonstrate that there is a strong correlation between mRNA levels and protein levels. Dr. Polakis states that in approximately 80% of the observations mRNA increases resulted in increased levels of protein. In addition, Dr. Polakis summarizes his experience in over 20 years of research that increases in mRNA levels are correlated with increases in protein levels. Applicants need not provide the data from each of Dr. Polakis' many experiments. Instead, Dr. Polakis has summarized the results obtained in his many experiments in his Declaration. As discussed above, the Hu reference does not contradict Applicants' position that it is more likely than not that differentially expressed mRNAs will result in differential levels of protein expresssion.

As discussed above, Applicants note that Dr. Polakis' is an expert in the field. In addition, whether or not increased mRNA levels correlate with increased polypeptide levels is an issue of fact. As discussed above, Declarations relating to issues of fact should not be summarily dismissed as "opinions" without an adequate explanation of how the Declaration fails to rebut the Examiner's position. *In re Alton* 76 F.3d 1168 (Fed. Cir. 1996). Furthermore, as discussed above, Applicants remind the PTO that "[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned." PTO Utility Examination Guidelines (2001) (emphasis added).

The Examiner asserts that the statements in the Ashkenazi Declaration did not demonstrate utility because there is no evidence whether the polypeptide is overexpressed. Applicants note that Dr. Ashkenazi's Declaration points out that regardless of whether a polypeptide encoded by a differentially expressed mRNA is itself differentially expressed, the polypeptide and antibodies thereto have utility as a diagnostic tool. As discussed above, it is Applicants' position that, in general, differential mRNA expression leads to differential polypeptide expression. Thus, Applicants maintain that it is more likely than not that the polypeptides recognized by the claimed antibodies are differentially expressed.

Applicants note that Dr. Ashkenazi is an expert in the field. In addition, whether or not increased mRNA levels correlate with increased polypeptide levels is an issue of fact. As discussed above, Declarations relating to issues of fact should not be summarily dismissed as "opinions" without an adequate explanation of how the Declaration fails to rebut the Examiner's position. *In re Alton* 76 F.3d 1168 (Fed. Cir. 1996). Furthermore, as discussed above, Applicants

remind the PTO that "[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned." PTO Utility Examination Guidelines (2001) (emphasis added).

The Examiner further asserts that the differential expression data may be an indication that the cancer tissue is aneuploid. As discussed above, the basis for the differential expression is irrelevant. The fact remains that the polypeptides recognized by the claimed antibodies are more likely than not to be differentially expressed and, as a consequence, the claimed antibodies possess utility.

The Examiner asserts that the Haynes and Hu references contradict Applicants assertion that there is a direct correlation between mRNA levels and the expression of the encoded protein. As discussed above, Applicants maintain that Haynes and Hu do not contradict Applicants' position that it is more likely than not that differential expression of an mRNA will result in differential expression of the encoded polypeptide.

The Examiner further maintains that Pennica supports the PTO's position that there is no correlation between DNA amplification and gene expression. As discussed above, the data in Example 18 demonstrate that the mRNAs encoding the polypeptides recognized by the claimed antibodies are differentially expressed and it is irrelevant whether the basis of this differential expression is gene copy number or different rates of transcription.

Applicants respectfully maintain that the diagnosis of stomach cancer or lung cancer is a substantial utility. In fact the Revised Interim Utility Guidelines promulgated by the PTO recognize that proteins which are differentially expressed in cancer have utility. (*See* the caveat in Example 12 which states that the utility requirement is satisfied where a protein is expressed in melanoma cells but not on normal skin and antibodies against the protein can be used to diagnose cancer.) In addition, while Applicants appreciate that actions taken in other applications are not binding on the PTO with respect to the present application, Applicants note that the PTO has issued several patents claiming antibodies to differentially expressed polypeptides or methods employing such antibodies. (*See, e.g.,* U.S. Patent No. 6,156,500 and U.S. Patent No. 6,562,343, attached hereto as Exhibits 8 and 9.) Thus, Applicants submit that they have established the utility of the claimed antibodies as a cancer diagnostic tool.

The Arguments made by the PTO are Not Sufficient to satisfy the PTO's Initial Burden of Offering Evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility"

As stated above, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

The PTO has not offered any arguments or cited any references to establish "that one of ordinary skill in the art would reasonably doubt" that the disclosed PRO1115 polypeptide is differentially expressed in stomach tumors or lung tumors and that antibodies which bind to the PRO1115 polypeptide can be used as a diagnostic tool. Given the lack of support for the PTO's position, Applicants submit that the PTO has not met its initial burden of overcoming the presumption that the asserted utility is sufficient to satisfy the utility requirement. And even if the PTO has met that burden, the Applicants' supporting rebuttal evidence is sufficient to establish that one of skill in the art would be more likely than not to believe that the claimed

antibodies can be used to generate antibodies useful as diagnostic tools for cancer, particularly stomach cancer or lung cancer.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Antibodies

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1115 gene and polypeptide in stomach tumor or lung tumor cells, along with the declarations and references discussed above, provide a specific utility for the claimed antibodies.

As discussed above, there are significant data which show that the gene for the PRO1115 polypeptide is more highly expressed in normal stomach tissue or normal lung tissue compared to stomach tumor or lung tumor respectively. These data are strong evidence that the PRO1115 gene and polypeptide are associated with stomach tumors or lung tumors. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the PRO1115 gene and polypeptide with specific diseases-stomach tumors or lung tumors. Accordingly, antibodies which bind to the PRO1115 polypeptide can be used as diagnostic tools for stomach tumors. Use as a diagnostic tool for cancer, particularly stomach cancer or lung cancer, is a specific utility – it is not a general utility that would apply to the broad class of antibodies.

Conclusion

The PTO has asserted that given the increase in amplified DNA (copy number) for PRO1115 in normal stomach tissue or normal lung tissue compared to stomach tumor or lung tumor respectively, one skilled in the art would not assume that a higher expression would correlate with increased mRNA or polypeptide levels. The PTO also asserts that mRNA over-expression does not correlate with protein over-expression.

First, the Applicants provided a first Declaration of Chris Grimaldi stating that the data in Example 18 are real and significant. This declaration also indicates that given the relative difference in expression levels, the disclosed polypeptides and antibodies which bind thereto have utility as cancer diagnostic tools. Applicants have also demonstrated that the data in Example 18 reflect mRNA levels rather than the chromosomal copy number of the gene

encoding PRO1115. The PTO has not offered any substantial reason or evidence to question the data in Example 18, or the first Grimaldi Declaration. Applicants have shown that the second Grimaldi Declaration and Polakis Declaration, the accompanying references, as well as the excerpts and references cited above, demonstrate that it is well-established in the art that a change in mRNA levels generally correlates to a corresponding change in the encoded protein levels. The PTO has not offered any substantial reason or evidence to question these declarations and supporting references. One of skill in the art will recognize that antibodies which bind to polypeptides differentially expressed in stomach cancer or lung cancer have utility as diagnostic tools for stomach cancer or lung cancer.

Finally, Applicants have pointed out that the substantial utilities described above are specific to the claimed antibodies because they are useful as diagnostic tools as a consequence of the differential expression of the PRO1115 polypeptide in stomach tumor cells or lung tumor cells compared to the corresponding normal stomach cells or normal lung cells respectively. This is not a general utility that would apply to the broad class of antibodies.

Given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed antibodies as diagnostic tools. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants remind the PTO that:

> A small degree of utility is sufficient . . . The claimed invention must only be capable of performing some beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely . . . A commercially successful product is not required . . . Nor is it essential that the invention accomplish all its intended functions . . . or operate under all conditions . . . partial success being sufficient to demonstrate patentable utility . . . In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed antibodies. In view of the

above, Applicants respectfully request that the PTO reconsider and withdraw the utility and enablement rejections.

Rejections Under 35 U.S.C. §103

Claims 1-5 were rejected as being unpatentable over Collier et al. Collier,Accession No. Q9BWY7, June 2001 in view of Turner et al. Accession No. AAX146414 (WO 0134804A1, published May 2001). As discussed in the response to the previous Office Action submitted on September 14, 2004, Applicants submit that because both of the cited references were published in 2001 they do not constitute prior art to the present application. In particular, as discussed above, the sequence of SEQ ID NO: 32 was first disclosed in US Provisional Application 60/090862 filed 6/26/1998 in Figure 1. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed antibodies, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35. Thus, Applicants are entitled to a priority date of at least **August 24, 2000**. Because each of the cited references were published after the priority date of the present application, they are not available as prior art against the present application. Accordingly, Applicants request that the PTO reconsider and withdraw the rejection under 35 U.S.C. §103.

Conclusion

The present application is believed to be in condition for allowance, and an early action to that effect is respectfully solicited. Applicants invite the Examiner to call the undersigned if any issues may be resolved through a telephonic conversation.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: July 26, 2005

By: Daniel Hart

Daniel Hart
Registration No. 40,637
Attorney of Record
Customer No. 30,313
(619) 235-8550